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Polysaccharide-specific B cell responses to vaccination in humans

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Keywords: antibody; B cells; B lymphocytes; glycoconjugate; immune response; polysaccharide; thymus-dependent; thymus-independent; vaccination

Abbreviations: B_{MEM}, memory B cells; PC, plasma cells; BCR, B cell receptor; LLPC, long-lived plasma cell; MenCCV, meningococcal serogroup C conjugate vaccine; MenCPS, meningococcal serogroup C polysaccharide vaccine; PCV-7, 7-valent pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine

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The introduction of vaccines containing the capsular polysaccharides of *N. meningitidis*, *S. pneumonia*, and *H. influenzae* type b has driven a significant reduction in cases of disease caused by these bacteria. The polysaccharide-specific antibody responses following vaccination are well characterized, however less is known about the B cells underlying this response. Here, we summarize the plasma cell (PC) and memory B cell (B_{MEM}) responses following plain polysaccharide and protein-polysaccharide conjugate vaccination, drawing together studies covering a range of vaccines and age groups. These studies show that infant primary PC and B_{MEM} responses to polysaccharide-conjugate vaccines are low in relation to older age groups but are significantly higher following booster doses. PC kinetics have generally been found to follow a similar pattern irrespective of vaccine type or age group, whereas divergent B_{MEM} responses have been reported following plain polysaccharide and conjugate vaccination. A degree of correlation between early B_{MEM} responses and maintenance of protective antibody levels has been identified in some studies, but the relationship between the 2 remains unclear. Identification of the B cell subsets involved and the mechanisms by which they are induced may provide a better understanding of the role of B cells in maintaining protective immunity through vaccination.

Introduction

Encapsulated organisms such as *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae* cause a significant burden of disease worldwide mainly affecting individuals at the extremes of age.^{1–3} The outer surface of all 3 bacteria is covered by a polysaccharide capsule, the composition and structure of which differs between and within each bacterial species. The polysaccharide capsule represents an important virulence factor, and is a major target for polysaccharide-specific antibodies that can be successfully generated by vaccines.⁴ There are 2 types of vaccines against these organisms which use the polysaccharide capsule as the vaccine antigen; plain polysaccharide vaccines and glycoconjugate vaccines. Natural immunity to encapsulated bacteria is provided by a combination of physical barriers, innate immune mechanisms and parts of the adaptive immune system including T cells and antibodies. Polysaccharide-containing vaccines aim to induce antigen-specific humoral immune responses, which can be quantified in terms of the serum antibody concentration. Antibodies are produced by B cells that have been triggered and activated by antigen and have undergone differentiation into antibody-secreting plasma cells. Plain polysaccharide vaccines act by cross-linking B cell receptors on the surface of naïve B cells, directing plasma cell production, whereas the protein component of glycoconjugate vaccines recruits T cell help and the generation of both plasma and memory B cells.⁴ Extracellular spaces, which have been invaded by pathogens

Table 1. Characteristics of studies describing plasma and memory B cell kinetics following immunization with glycoconjugate vaccines

Study reference	Age (y)	Number of samples per study time point*	Vaccine	Carrier protein	Number of priming doses [time since last vaccination]	Study time points (days)
Plasma cells						
Kelly et al. ⁷	13–15	3–34	MenCCV	CRM ₁₉₇	1 [2–3 y]	0, 3, 4, 5, 6, 7, 8, 9, 10, 12, 28
Clutterbuck et al. ⁶	28–44	6	PCV-7†	CRM ₁₉₇	1 [1 y]	0, 6, 7, 15
Blanchard Rohner et al. ⁵	1	5–26	MenCCV	CRM ₁₉₇	3 [8 mo]	0, 2, 4, 6, 8, 9, 30
Kelly et al. ⁸	0.17	33	MenCCV	CRM ₁₉₇	-	4, 6, 8, 10, 12, 14, 16, 30
Kelly et al. ⁸	0.33	29	MenCCV	CRM ₁₉₇	2 [1 mo]	4, 6, 8, 10, 12, 14, 16
Memory B cells						
Kelly et al. ⁷	13–15	3–40	MenCCV	CRM ₁₉₇	1 [2–3 y]	0, 3, 4, 5, 6, 7, 28, 365
Clutterbuck et al. ⁶	28–44	6	PCV-7†	CRM ₁₉₇	1 [1 y]	0, 6, 7, 15, 28
Blanchard Rohner et al. ⁵	1	4–28	MenCCV	CRM ₁₉₇	3 [8 mo]	0, 2, 4, 6, 8, 9, 30
Kelly et al. ⁸	0.17	31	MenCCV	CRM ₁₉₇	-	4, 6, 8, 10, 12, 14, 16, 30
Kelly et al. ⁸	0.33	17	MenCCV	CRM ₁₉₇	2 [1 mo]	4, 6, 8, 12, 14, 16, 30
Perrett et al. ⁹	7	52	MenCCV	TT	3 [6 y]	0, 7, 28, 365
Perrett et al. ⁹	8	25	MenCCV	TT	2 [6 y]	0, 28, 365
Perrett et al. ⁹	8.3	53	MenCCV	TT	1 [6 y]	0, 7, 28, 365
Perrett et al. ⁹	9.3	30	MenCCV	TT	1 [6 y]	0, 28, 365
Perrett et al. ⁹	10.3	27	MenCCV	TT	1 [6 y]	0, 28, 365
Perrett et al. ⁹	11.3	27	MenCCV	TT	1 [6 y]	0, 28, 365
Perrett et al. ⁹	12.1	29	MenCCV	TT	1 [6 y]	0, 7, 28, 365

*Number of samples between study time points may differ markedly and the range is given if known, otherwise the total number of samples is shown;

†Values from serotype 4 were used to describe plasma and memory B cell kinetics; CRM₁₉₇, cross-reactive material (non-toxic recombinant form of diphtheria toxin); MenCCV, meningococcal serogroup C conjugate vaccine; PCV-7, 7-valent pneumococcal conjugate vaccine; TT, tetanus toxoid.

and which are usually the place where they multiply, are protected by antibodies which kill extracellular microorganisms through complement-mediated bacteriolysis, opsonophagocytosis, or antibody-dependent cellular cytotoxicity.

Although there are some data indicating how best to achieve high concentrations of (functional) antibodies, little is known about the B cells that underlie such an immune response. Circulating B cells are a dynamic population and previous studies have defined the kinetics of the B cell response and permitted B cell frequencies before and after immunization to be related to immediate and medium-term antibody responses. In this manuscript we aim to describe the kinetics (timing of responses) and magnitude of both polysaccharide-specific plasma cell (PC) and memory B cell (B_{MEM}) responses following vaccination, summarizing data

from previous studies in children, adolescents, and adults.^{5–13} Table 1 shows characteristics of studies describing plasma and memory B cell kinetics following glycoconjugate vaccination. Data derived from these studies were used to generate Figures 1 and 2.

B Cell Kinetics Following Vaccination

Plasma cell kinetics

Most studies that aimed to determine polysaccharide-specific B cell frequencies were performed using the enzyme-linked immunospot (ELISpot) assay. Other approaches such as flow-cytometry have only rarely proven to be helpful and are also costly, laborious, and difficult to perform on the large scale needed in clinical vaccine trials.^{14,15}

PCs may be detected in peripheral blood using an ex-vivo ELISpot. This technique involves measurement of the frequency of antibody-secreting cells in peripheral blood which spontaneously produce antibody.⁶ In the steady-state, antigen-specific PCs in the peripheral blood are only present at a very low overall frequency in comparison to the total B cell population, but rise transiently following vaccination. PC kinetics following primary vaccination have been investigated in children after the first and third dose of a 3 dose schedule of meningococcal serogroup C conjugate vaccine at 2, 3, and 4 mo of age (MenCCV).⁸ Following the first vaccination, PCs were low frequency but peaked at day 10 and fell to undetectable levels by day 30. PC responses following the third dose were faster both in onset and decline, with the highest frequencies detected on day 4 (the first day assessed)

and reaching baseline for all but one individual by day 12. At the time of the third dose, germinal centers generated by the previous vaccine doses may still be present, having not yet undergone the process of involution. Therefore, revaccination may continue to drive a response from these germinal centers, accounting for the early peak in plasma cells.

A small but consistent second rise of MenC-specific PCs was seen both in unprimed individuals after the first vaccine dose and following the third dose detectable at day 16 and day 12, respectively.⁸ Although only a few samples were available for testing at each time point, it is possible that these later peaks represent the time of germinal center involution as suggested by animal data.¹⁶

Unprimed B cell responses directed at polysaccharides are more difficult to assess in adults. This is because the majority of vaccine-naïve adults already have pre-existing immunity to capsular polysaccharides, which also serve as vaccine antigens.^{10,13,14} This immunity, in the form of B_{MEM} and serum antibody is probably acquired following repeated nasopharyngeal carriage of encapsulated bacteria. To overcome this problem, a novel T-dependent protein antigen for unvaccinated individuals in the UK, the rabies vaccine, was used to investigate B cell kinetics in a controlled setting of primary, secondary and tertiary immune responses.¹² In this study, PCs peaked at day 10 following priming, with the most rapid and highest PC responses seen at day 7 following the third dose in the naïve group, as was observed with the primary polysaccharide response in infants. Studies of adult PC kinetics following influenza vaccination have also revealed consistent patterns of response. In these studies, PCs peaked at around a week following immunization.¹⁷⁻¹⁹

The PC response to a booster dose of a glycoconjugate vaccine is more rapid than following a primary dose, similar to the PC kinetics following repeated protein vaccination. The peak in PC responses following booster vaccination with a MenC glycoconjugate in 1-y-old children⁵ or 13- to 15-y-old adolescents⁷ appeared at day 6, which is more rapid than following the first vaccine dose in infants but slower

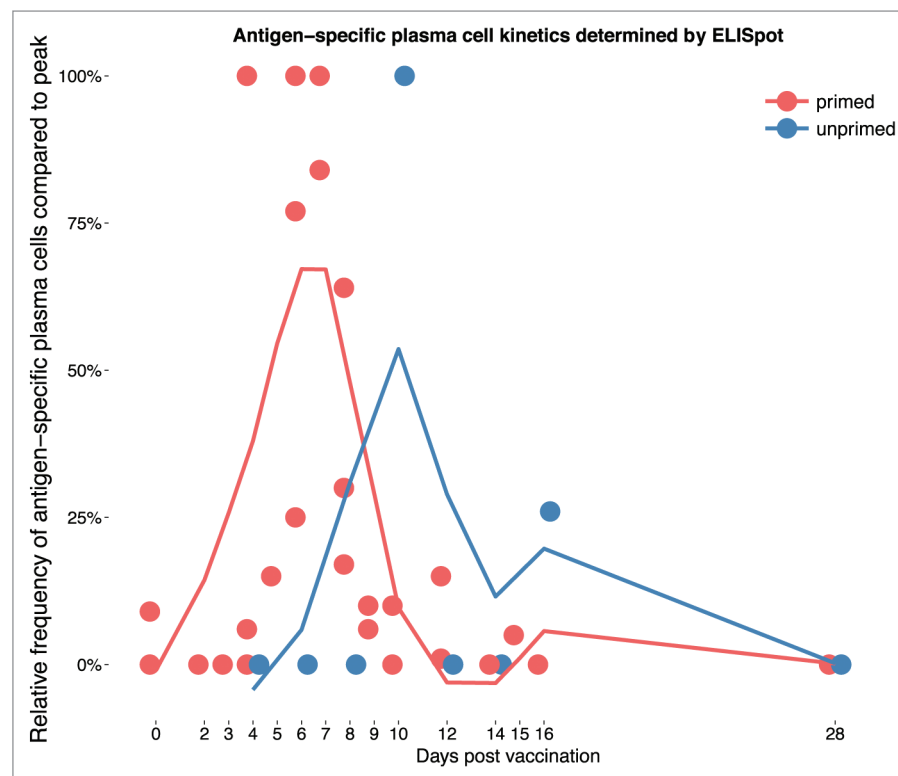


Figure 1. The kinetics of the plasma cell response to polysaccharide-containing vaccines in vaccine primed and unprimed subjects. Data taken from studies reporting on at least 2 time points between baseline and 1 mo following vaccination.⁵⁻⁸ Values are plotted as a percentage of the maximum response within the observed time period and then smoothed (using a locally weighted polynomial regression model [method "loess"] of the ggplot2 package²⁰ in R²¹) across all 4 studies represented by the lines for vaccine primed and unprimed infants, respectively.

than that following the third dose of an infant primary series.⁸

Given as a booster dose, both plain polysaccharide and glycoconjugate vaccines produce a similar pattern of PC responses. No difference in polysaccharide-specific PC kinetics was found between adolescents receiving a booster dose of MenCCV or MenC polysaccharide vaccine (MenCPS).⁷ Furthermore, studies of glycoconjugate vaccines have demonstrated similar PC kinetics for both polysaccharide and carrier protein antigens,^{6,8} although one study reported a more rapid decrease in meningococcal serogroup C (MenC) than diphtheria toxoid-specific PCs.⁵

The kinetics of PC responses to vaccination in primed (individuals with pre-existing immunity through previous vaccination) and unprimed children and adults compiled from studies reporting on several separate time points within

the first month following vaccination are summarized in Figure 1.

Memory B cell kinetics

Culturing peripheral blood mononuclear cells (PBMCs) with polyclonal stimulators such as a combination of pokeweed mitogen, *S. aureus* Cowan strain and CpG DNA induces the proliferation of B_{MEM} and their differentiation into antibody-secreting cells which can be detected using the ELISpot assay.^{6,22} The culture step means that the output of the ELISpot assay is not a direct measure of B_{MEM} frequency in the peripheral blood, but is useful for the comparison of responses between individuals and time points in relation to vaccination. Other methods such as flow cytometry or a limiting dilution assay may also be used to enumerate antigen-specific B_{MEM} , however labeling of polysaccharide antigens for flow cytometric analysis is very laborious and not straight forward due to potential

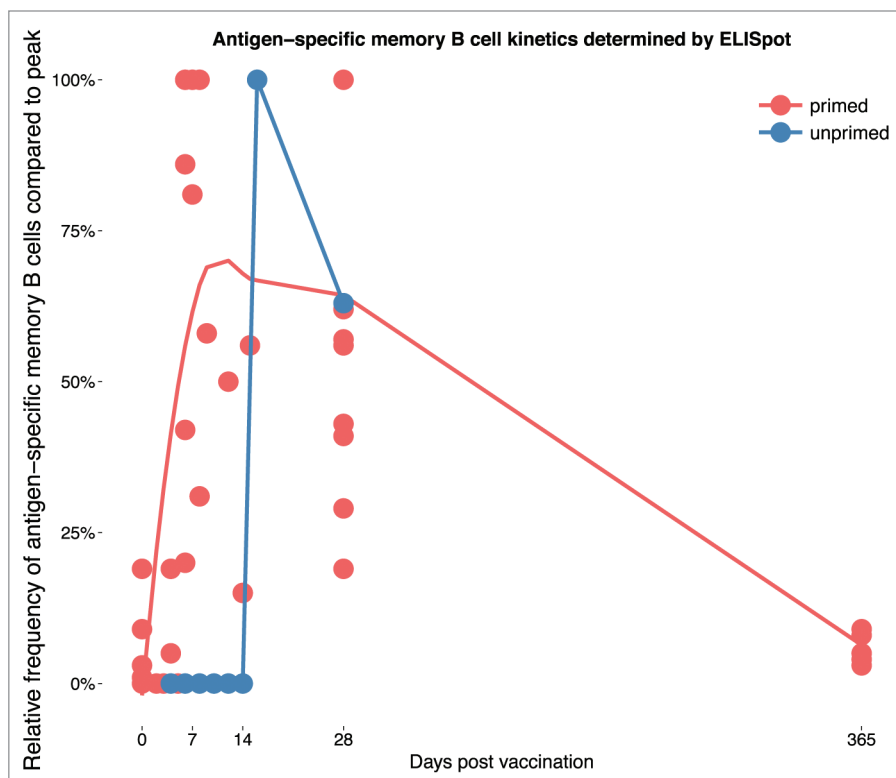


Figure 2. The kinetics of the memory B cell response to polysaccharide-containing vaccines in primed and unprimed individuals. Data taken from studies reporting on at least one additional time point other than baseline and 1 mo post-vaccination.⁵⁻⁸ Values are plotted as a percentage of the maximum response within the observed time period and then smoothed (see Figure legend 1; for the "unprimed" group data points were directly connected as smoothing in a similar way was not possible) across all 5 studies represented by the lines for vaccine primed and unprimed individuals, respectively.

non-specific binding of B cells, and the limiting dilution assay is not as sensitive as ELISpot for B_{MEM} detection.²³

B_{MEM} responses to a first infant dose of glycoconjugate vaccine are low, with MenC specific B_{MEM} only appearing at day 14 post-vaccination with numbers close to the limit of detection.⁸ Reflecting the PC response, B_{MEM} responses to a third dose of vaccine are more rapid, becoming detectable at day 4.⁸ As described previously, primary B cell responses to polysaccharide antigens are difficult to study in adults, however, using rabies protein as a model vaccine, B_{MEM} responses in unprimed adults vaccinated with rabies protein vaccine showed similar kinetics; the first B_{MEM} became detectable 10 d post-vaccination but appeared more rapidly following additional doses.¹²

Following booster vaccination with a glycoconjugate vaccine at one year of age, B_{MEM} were shown to peak at around a week,⁵ which is similar to booster

responses in adults primed with rabies vaccine.¹² When booster doses of MenCPS and MenCCV were compared in adolescents, B_{MEM} responses were more rapid and better sustained in those given the glycoconjugate vaccine as a booster.⁷

Compared with PC responses, B_{MEM} responses in peripheral blood are more prolonged. Although frequencies of B_{MEM} also diminish following the post-vaccination peak, B_{MEM} specific to polysaccharides^{6,14} as well other antigens such as the smallpox virus²⁴ have been detected in peripheral blood months to years following vaccination. B_{MEM} generated in germinal center responses are thought to circulate briefly in peripheral blood before transiting to secondary lymphoid organs such as the lymph nodes or spleen where they persist long-term, or from where they continue to recirculate.⁴ It is therefore important when interpreting the studies described in this paper to appreciate that B cells are only being measured in transit.

There is currently limited knowledge of B cell activity in other compartments; however the inaccessibility of these tissues makes peripheral blood the only option in most cases.

Figure 2 combines data from the studies discussed in this section to summarize the B_{MEM} response to vaccination in primed and unprimed individuals.⁵⁻⁹

Frequency of Polysaccharide-Specific B Cell Responses

Although the timing of B cell responses seems to adhere to general patterns (Figs. 1 and 2), the magnitude of these responses is more variable. In the following section we address the effect of factors such as the number of vaccine doses, age at vaccination, and vaccine type on post-vaccination B cell frequencies.

Plasma cell frequency following vaccination

As well as becoming increasingly rapid, the magnitude of the PC response is also greater with additional doses of vaccine after the primary dose. A greater frequency of PCs is generated following the third dose of MenCCV than following the first,⁸ although in toddlers receiving their first dose of pneumococcal conjugate vaccine at 12 mo of age, revaccination at 14 mo did not increase PC frequency in peripheral blood relative to the same time point (1 wk post-vaccination) at 12 mo.¹⁰

Despite showing similar kinetics, there are differences in the number of plasma cells induced by plain polysaccharide and glycoconjugate vaccines. In adolescents receiving either a booster dose of MenCCV or MenCPS, both of which contained the same quantity of polysaccharide antigen, the PC response was of greater magnitude in the glycoconjugate group, although there were no differences in the timing of responses.⁷ This suggests that a single signal from the polysaccharide component of both vaccine types is sufficient to induce the generation of PCs from pre-existing B_{MEM} , but that T cell help may facilitate greater expansion of the PC pool.

Differences in PC frequency have also been reported in adults following different combinations of the 7-valent pneumococcal conjugate vaccine (PCV-7) and the

23-valent pneumococcal polysaccharide vaccine (PPV-23). In adults primed with PCV-7, boosting with PPV-23 resulted in a significantly higher PC response on day 7 compared with boosting with PCV-7.²⁵ This may be because the polysaccharide quantity of each serotype is more than 10 times higher in the PPV-23 compared with the PCV-7 or may result from unconjugated polysaccharide antigens inducing the terminal differentiation of B_{MEM} into PCs, a phenomenon which will be covered in more detail in the discussion of B_{MEM} responses below.

Memory B cell frequency following vaccination

B_{MEM} frequencies differ depending on the number of vaccine doses, and particularly when plain polysaccharide and glycoconjugate vaccines are compared in infants and the elderly. Greater B_{MEM} frequencies have been reported following a 3 dose⁸ compared with a 2 dose primary series¹¹ of meningococcal conjugate vaccine, however in both studies less than 30% of children still had detectable polysaccharide-specific B_{MEM} by 12 mo of age. Despite low pre-booster B_{MEM} frequency, robust responses have been reported following booster vaccination with glycoconjugate vaccines at 12 mo of age,^{5,11} suggesting that the small pool of B_{MEM} maintained post-priming is sufficient to sustain immunological memory.

The effect of age on B_{MEM} frequencies has been investigated in a number of studies. Greater frequencies of B_{MEM} have been found following vaccination in adults than in children. Twelve month old toddlers with little or no prior exposure to encapsulated bacteria required at least 2 doses of PCV-7 to reach B_{MEM} frequencies equivalent to those following a single dose in adults.¹⁰ However, all of the adults in this study already had detectable polysaccharide-specific B_{MEM} at baseline, likely induced by prior pneumococcal colonization, in effect priming the immune system. Another study reported that age at primary vaccination (ranging between 6 mo and 34 y) with a glycoconjugate did not affect the induction and persistence of polysaccharide-specific B_{MEM} .¹⁴

There are no studies describing B_{MEM} kinetics following plain polysaccharide vaccination in children. Plain

polysaccharide vaccines are thymus-independent (T-independent) antigens, and are not thought to induce B_{MEM} formation. Instead, they are believed to act by inducing extensive cross-linking of the B cell receptor (BCR) on marginal zone B cells and B1 cells, inducing an extrafollicular response predominantly involving PCs.²⁶ Children under the age of 2 y are unable to make an efficient immune response to T-independent antigens such as plain polysaccharide vaccines. This phenomenon is not well understood but present models suggest (1) an immaturity of most B cells, e.g., lack of CD21/complement receptor 2 on neonatal B cells,²⁷⁻²⁹ (2) differences in activation requirements between primary and secondary B cells with young children having primary B cells that require both BCR signaling and T cell help for activation,³⁰ (3) low frequency of marginal zone B cells,^{31,32} (4) lower levels of complement C3, and (5) immaturity of marginal zone dendritic cells and the marginal zone in young children.³³

Although there are no data in infants, B_{MEM} responses to plain polysaccharide and glycoconjugate vaccines have been compared when given to adolescents and adults. In adolescents, the magnitude of B_{MEM} response was greater following a booster dose of MenCCV than a booster of MenCPS.³⁴ In an adult study, vaccination with PCV-7 resulted in an increase in polysaccharide-specific B_{MEM} whereas vaccination with PPV-23 had the opposite effect, causing a reduction in B_{MEM} frequency.²⁵ Adults over the age of 65 are the only population to routinely receive PPV-23. This vaccine appears to offer a degree of short-term protection against invasive pneumococcal disease,³⁵ but no reduction in rates of pneumonia or mortality.^{36,37} Furthermore, immunization with plain polysaccharide vaccines may reduce antibody levels induced by prior receipt of a polysaccharide-containing vaccine, an effect known as hyporesponsiveness. This phenomenon has been demonstrated in children³⁸ and more recently in adults,³⁹ although another smaller adult study did not identify an effect.¹³ Hyporesponsiveness may be explained by the effect of polysaccharide vaccines on the B_{MEM} population. Plain polysaccharide vaccines are thought to deplete

the B_{MEM} pool by inducing strong BCR cross-linking and driving the terminal differentiation of these cells into PCs,²⁵ or by inducing apoptosis as demonstrated in neonatal mice primed with MenCCV and boosted with MenCPS.⁴⁰ A recent study identified IgM-producing B cells as an important subset in the response to PPV-23 in young adults.⁴¹ When the B cell response was compared between young and elderly adults, elderly participants had fewer IgM positive B cells and an impaired IgM response to vaccination. A shift in B cell populations has also been implicated in the increased susceptibility of HIV-infected children to pneumococcal disease.⁴² Here, children with HIV were found to have reduced numbers of circulating mature, naïve and resting B_{MEM} , with an over-representation of mature, activated B cells.

Correlation of B Cell Responses to Antibody Concentrations

On a population scale a relationship between antibody concentration and clinical protection has been demonstrated, such that (functional) antibody concentrations are routinely used to predict vaccine efficacy in clinical vaccine trials. For example, the recently introduced pneumococcal conjugate vaccine, PCV-13, was licensed on the basis of its ability to elicit antibody responses above a threshold defined by the efficacy of PCV-7.⁴³ Plasma cells have been shown to correlate with immediate increases in antibody^{5,7} however long-term maintenance of serum antibody cannot be accounted for by transiently induced PCs. Instead, it is thought to rely upon B_{MEM} and long-lived PCs (LLPCs) induced by immunization. LLPCs have been identified in mice as a fraction of the PC population produced in the germinal center reaction following protein-polysaccharide vaccination.⁴⁴ These cells persist in the bone marrow and can secrete antibody for prolonged periods of time. Support for the existence of LLPCs in humans comes from observations including the report that humans depleted of PC precursors (and hence circulating PCs) with rituximab are still able to maintain normal antibody levels.⁴⁵ There is still

debate on the exact mechanisms of survival and maintenance of LLPCs, however the “imprinting lifespan” theory appears to best fit the observed antibody kinetics in humans. This theory suggests that PC life span is dependent on the strength of combined B cell signals experienced by the cell during the encounter with antigen.⁴⁶ Mechanisms of long-term maintenance of B_{MEM} are also still unclear but most likely rely on antigen-independent processes.⁴⁷

While some studies have demonstrated a relationship between B_{MEM} and antibody concentration at various intervals after immunization this has not been consistent for all antigens or between studies.⁹ Blanchard Rohner et al. found that B_{MEM} levels rather than antibody levels following priming with MenCCV better discriminated those with putative protective antibody levels at 12 mo.⁵ Another study identified a weak positive correlation between 5 mo B_{MEM} levels and 12 mo antibody concentrations for serotypes C and Y but not A or W in children vaccinated at 2 and 4 mo of age with the MenACWY-CRM₁₉₇ conjugate vaccine.¹¹

In the absence of pre-existing antibody, the secondary immune response initiated by memory cell populations is too slow to prevent infection by encapsulated bacteria, which can become established within hours or days. Even a large B_{MEM} response may not guarantee protection; pneumococcal conjugate vaccines have so far failed to provide any protection against serotype 3 disease despite large B_{MEM} responses generated toward this serotype in children vaccinated with a serotype 3-containing vaccine.⁴⁸

Herd immunity induced by polysaccharide-containing vaccines is dependent on the presence of polysaccharide-specific antibody in the nasopharyngeal mucosa, which prevents bacterial colonization and carriage. The generation of antibody concentrations of sufficient magnitude to prevent colonization requires B_{MEM} to be resident in the mucosa, however polysaccharide-specific B_{MEM} are not found in this tissue at the steady-state, only appearing transiently following vaccination.⁴⁹ This may limit the duration of herd immunity provided by glycoconjugate vaccines. Protein-specific B_{MEM} appear to persist better in the mucosa

than polysaccharide-specific B_{MEM}, perhaps reflecting the different immunological properties of the stimulating antigen. It will be interesting to compare the extent of herd immunity and the effects on carriage provided by the recently licensed protein-based serogroup B meningococcal vaccine with that provided by glycoconjugate vaccines for other meningococcal capsular groups.

Conclusions and Perspectives

The ability to detect B cells in the circulation using techniques such as ELISpot has allowed the study of how 2 major B cell populations, plasma cells and memory B cells, respond to vaccination. Consistent patterns have been revealed applicable to a range of ages and vaccine types. Despite efforts to correlate peripheral B cell responses with antibody levels, only weak relationships have so far been identified. This is not surprising, given the incomplete understanding of the long-term activity and maintenance of B cells following their relatively short appearance in peripheral blood. Further understanding of the role of B cells in the post-vaccination immune response requires certain challenges to be overcome. First, the ELISpot assay as it is currently performed suffers from the limitation that B_{MEM} can only be easily measured in the peripheral blood. In contrast to antibodies, which are secreted into the serum as their site of action, B_{MEM} only pass through the blood on their way to the secondary lymphoid tissues where they reside and meet their antigen. Further, detection of PCs and B_{MEM} in peripheral blood may be limited by the sensitivity of the available assays, and some responses especially in young children may be below the limit of detection. The reliability of the assays used to measure B cell frequency is also an important consideration. Data indicate that the cultured ELISpot assay for the detection of B_{MEM} is reliable across operators and laboratories (Trück et al., unpublished observations), however protocols may need to be standardized before data from multiple centers can be compared. A further challenge is the identification of the B cell subsets involved in the

response to vaccination. T-dependent and T-independent antigens induce different subsets of B cells,^{15,49} but the mechanisms by which each antigen drives its signature B cell phenotype is unclear, as is the contribution of each subset to the maintenance of serum antibody. Identification of the subsets involved may allow prediction of the duration of protection and clinical outcomes such as efficacy and carriage using early B cell responses as a surrogate marker of immunity. An understanding of the signals influencing the induction of each subset may lead to the development of new vaccine strategies, which are more effective at preventing carriage and maintaining herd immunity. In conclusion, B cells are key players in the induction and maintenance of vaccine-induced immunity. A better understanding of the phenotype and role of the B cell subsets involved has the potential to provide a useful new tool for predicting the effectiveness and duration of vaccine-induced immunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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